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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,978	11/24/2003	Gregg Budahazi	1530.0550001/JUK/JCI	1745

26111 7590 01/23/2009

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	
MAIL DATE	DELIVERY MODE
01/23/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/719,978	BUDAHAZI ET AL.	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-40* is/are pending in the application.

4a) Of the above claim(s) *1-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed October 20, 2008. Claims 1-40 were previously pending, with claims 1-20 withdrawn from consideration. Applicants amended claims 21, 22 and 40. Claims 21-40 will be examined.

2. The rejection of claims 30-39 under 35 U.S.C. 102(b) as anticipated by Nochumson et al. and the rejection of claims 21-29 and 40 under 35 U.S.C. 103(a) over Nochumson et al., Kvederas et al. (US 2003/0109696 A1) and Cooke et al. is withdrawn in favor of new rejections. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" below.

3. This office action is made non-final because of new grounds for rejection regarding new matter and written description, as well as for claims 30-39.

Response to Arguments

4. Applicant's arguments filed October 20, 2008 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 30-39 under 35 U.S.C. 112, second paragraph, that the claims are not indefinite, since "any impurities in the claimed DNA products are so minute that LAL assay, Southern blot assay, chromatography, Northern blot assay and ethidium bromide analysis are simply not sensitive enough to detect them under any conditions" (page 8 of the response).

However, claims 30-39 are not dependent from claim 21 or any other claim listing specific concentrations of impurities, and claim 30 does not list any specific levels of impurities. Therefore, a limitation "undetectable by Southern blot assay", for example, does not provide guidance of what the concentration of the impurity is, considering that the amount of DNA detectable by Southern

blot depends on the hybridization conditions such as temperature and salt concentration as well as on the total amount of DNA tested and the amount of background DNA present in the sample. Thus, such limitation does not provide metes and bounds for the level of DNA impurities in the plasmid preparation. The same argument holds true for all of the other detection methods listed in these claims.

The rejection is maintained.

B) Applicants' arguments regarding the interpretation of the term "about" were mostly addressed before. Further, none of the rejections are based on the interpretation of this term, since the concentrations of impurities taught by Nochumson et al. are within the claimed ranges or very close to the claimed values.

C) The rejection of claims 21-29 and 40 has been revised, and the rejection of claims 30-39 has been withdrawn, therefore Applicants' arguments are moot.

Claim Rejections - 35 USC § 112, new matter

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 21-29 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

A) The following limitations of claims 21, 22 and 40 do not have support in the specification or in the originally filed claims: "about 0.00001% to about 0.0001% RNA".

The specification discloses, on pages 19 and 20, paragraphs [0068] and [0069], the following RNA concentrations: "less than about 5% by weight of RNA, such as, e.g., about 5% by weight of RNA to about 0.00001%, or less than 0.0001%", " less than about 5% by weight of RNA". Therefore there is no support for the claimed range of RNA concentration in the originally filed disclosure.

B) The following limitations of claim 22 do not have support in the specification or in the originally filed claims: "from about 0.00004 μg to about 0.0004 μg host DNA per μg DNA product" and "from about 0.00001 EU to about 0.0001 EU per mg DNA product."

The specification discloses, on pages 19 and 20, paragraphs [0068] and [0069], the following host DNA amounts: "less than about 0.002 μg of host DNA/μg of DNA product, such as, e.g., about 0.002 μof host DNA/μg of DNA product to about 0.00002 μg of host DNA/μg of DNA product, or less than 0.00004 μg of host DNA/μg of plasmid DNA", "less than about 0.002 μg of host DNA/μg of DNA product".

The specification discloses, on pages 19 and 20, paragraphs [0068] and [0069], the following endotoxin amounts: "less than about 0.01 EU/μg of DNA product, such as, e.g., about 0.0001 EU/μg to about 0.0002 EU/μg" and " less than about 0.01 EU/μg of DNA product".

Therefore, the claimed ranges of host DNA contamination and EU contamination do not have support in the disclosure as originally filed.

In conclusion, the above listed limitations of claims 21-29 and 40 introduce new matter to the claims.

Claim Rejections - 35 USC § 112, written description

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 21-29 and 40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 21 is drawn to a DNA product comprising from about 95% to about 100% of circular plasmid DNA, wherein said DNA product contains from about 0.00001% to about 0.0001% RNA; from about 0.00002 μg to about 0.002 μg host DNA per μg DNA product; from about 0.00000001 μg to about 0.001 μg protein per μg DNA product; and wherein said DNA product contains less than 0.01 Endotoxin Units (EU) per μg of DNA product.

Claim 22 is drawn to the product of claim 21, where said DNA product contains from about 0.00001% to about 0.0001% RNA; from about 0.00004 μg to about 0.0004 μg host DNA per μg DNA product; and wherein said DNA product contains from about 0.00001 EU to about 0.0001 EU per μg of DNA product.

Claims 23-27 are drawn to different levels of RNA, host DNA and EU levels.

However, there is no support in the specification or claims as originally filed for the claimed product. The specification discloses, on pages 19 and 20, paragraphs [0068] and [0069], the following DNA products:

"The DNA product obtained by the process of the invention can comprise about 95% or greater by weight of circular plasmid DNA, wherein said DNA product contains less than about 5% by weight of RNA, less than about 0.002 μg of host DNA/μg of DNA product, less than about 0.001 μg of protein/μg of DNA product, and less than about 0.01 EU/μg of DNA product."

The following plasmid DNA products were obtained by Applicants in the Examples:

A) Example 1: DNA product with 0.0004 μg of host DNA/μg of DNA product and 0.0002 EU/μg of DNA product. No RNA or protein levels were specified. No percentage of circular plasmid DNA was specified.

B) Example 2: DNA product with 0.00025 μg of host DNA/μg of DNA product and 0.0002 EU/μg of DNA product. No RNA or protein levels were specified. No percentage of circular plasmid DNA was specified.

C) Example 3: DNA product with 0.00029 μg of host DNA/μg of DNA product and 0.00001 EU/μg of DNA product. No RNA or protein levels were specified. No percentage of circular plasmid DNA was specified.

D) Example 4: DNA product with 0.001 μg of host DNA/μg of DNA product and 0.0006 EU/μg of DNA product. No RNA or protein levels were specified. No percentage of circular plasmid DNA was specified.

E) Example 5: DNA product with 0.0002 μg of host DNA/μg of DNA product and 0.00019 EU/μg of DNA product, with 92% of supercoiled DNA. No RNA or protein levels were specified. The average of four purifications resulted in DNA product with 0.0005 μg of host DNA/μg of DNA product and 0.0001 EU/μg of DNA product, with 90% of supercoiled DNA. No RNA or protein levels were specified.

The original claim 30 read as follows:

"A DNA product comprising about 95% or greater by weight of circular plasmid DNA, wherein said DNA product contains less than about 5% by weight of RNA, less than about 0.002 μg

of host DNA/μg of DNA product, less than about 0.001 μg of protein/μg of DNA product, and less than about 0.01 EU/μg of DNA product."

Therefore taking into account the original disclosure as well as the experimental examples, there is no evidence that Applicants were in possession of the DNA products as claimed in claims 21-29 and 40, especially with respect to the degree of RNA and protein removal.

Claim Rejections - 35 USC § 112, second paragraph

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 30-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 30-39 are indefinite in claim 30. Claim 30 is indefinite over the recitation of "wherein said DNA product contains an amount of host cell derived impurities that is undetectable by any one of a group consisting of: LAL assay, Southern blot assay, chromatography, Northern blot assay, and ethidium bromide agarose analysis."

It is not clear what are the meets and bounds of this claim. As the detection limit of any particular assay depends on the conditions under which it is performed as well as the ingredients used, the level of impurities detected will depend on where and how the assay is performed. Applicants did not specify conditions and cutoff values for any of these assays which would result in undetectable levels of impurities.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 30-39 are rejected under 35 U.S.C. 102(b) as being anticipated by Marquet et al. (WO 95/21250; cited in the IDS).

Regarding claims 30-39, Marquet et al. teach plasmid DNA and pharmaceutical preparation (page 30-32), where the levels of RNA, host protein, endotoxin and host DNA are undetectable by gel electrophoresis, BCA analysis, LAL analysis and Southern blot, respectively, and where the preparation is free of pyrogens (page 31, Table). They teach pharmaceutical preparations and sterile containers (page 2, lines 24-25; page 3, lines 21-24; page 4, lines 17-19; page 15, lines 28-31; page 16, lines 1-3).

Claim Rejections - 35 USC § 103

13. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 21-29 and 40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nochumson et al. (US 2001/0034435 A1; cited in the IDS and in the previous office action), Kvederas et al. (US 2003/0109696 A1; cited in the previous office action), Cooke et al. (J. Biotechnol., vol. 85, pp. 297-304, February 2001; cited in the previous office action), Lee et al.(WO 96/02658; cited in the IDS) and Lander et al. (WO 01/46215; cited in the IDS).

A) Regarding claims 21-29 and 40, Nochumson et al. teach plasmid DNA and pharmaceutical preparation (page 8, [0099]). Nochumson et al. teach plasmid DNA preparation with 95% plasmid DNA and less than 5% RNA (page 8, [0099]). Nochumson et al. teach plasmid DNA preparation with 0.05% of host DNA (page 8, [0099]), which is equivalent to 0.0005 μg of host DNA/μg of DNA product, therefore Nochumson et al. anticipate the range from about 0.00002 to about 0.002 μg of host DNA/μg of DNA product (claim 21 and 40) and the amount of 0.0005 μg (page 27), and about 0.0004 μg (claim 22), since Applicants did not define the range corresponding to the term "about". Nochumson et al. teach plasmid DNA preparation with less than 0.06% of protein (page 8, [0099]), which is equivalent to 0.0006 μg of protein/μg of DNA product, therefore Nochumson et al. anticipate the range from about 0.00000001 to about 0.001 μg of protein/μg of DNA product (claims 21, 22, 40). Nochumson et al. teach plasmid DNA preparation with less than 0.2EU/mg of endotoxin, which equals less than 0.0002 EU/μg of DNA product (page 8, [0099]), anticipating the range of less than 0.01 EU/μg (claim 21) as well as the amount of 0.0002 EU/μg (claim 25) and the range from about 0.00001 EU to 0.0001 EU/μg of DNA product (claims 22 and 26, since the term "about" was not defined and 0.0002 EU is reasonably close to 0.0001 EU) as well as the range from about 0.0001 EU to 0.0002 EU/μg of DNA product (claim 40). They teach pharmaceutical preparations (claims 8, 11, 19, 31).

B) Nochumson et al. do not teach RNA contaminant levels from about 0.00001% to about 0.0001% or 0.00004 μg of host DNA/μg of DNA product.

C) The references cited below show that different levels of impurities in plasmid DNA can be obtained depending on the type of purification method used. Kvederas et al. teach a method of plasmid DNA purification from bacterial cells which results in a removal of bacterial RNA from the preparation to undetectable levels (Abstract; page 14, 15, Tables 3 and 4). Other impurity levels were as follows (Table 3): 0.035 EU//μg of DNA product and 0.000000346 μg of host protein/μg of DNA product.

Cooke et al. teach removal of RNA from plasmid preparations using host cells expressing a ribonuclease (Abstract; page 299, second paragraph).

Lee et al. teach a plasmid preparation with 0.029 μg of host DNA/μg of DNA product, less than 0.01 μg of protein/μg of DNA product, less than 0.01% RNA and 0.0028 EU/μg of DNA product (page 17, Table 1). Lander et al. teach a plasmid DNA product with undetectable protein content, 0.00003 EU/μg of DNA product EU/μg of DNA product and 0.043% RNA (Table 4, page 35).

Therefore it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have further purified the plasmid of Nochumson et al. to achieve the desired impurity levels, since, as indicated by the cited references, the level of impurities obtained depended on the purification method, and thus could be achieved by routine optimization. It would have been prima facie obvious to perform routine optimization using reagents and purification procedures, as noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable

ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection specific contamination levels was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

The motivation to remove RNA to undetectable levels was provided by Kvederas et al. (page 1, [0005]):

"One feature, however, is that certain substances present in the bacterial biomass, among them polysaccharides derived from the bacterial cell wall, lipopolysaccharides and RNA, are difficult to remove without several chromatographic steps, and tend to contaminate the standard DNA preparations. Some of these bacterially derived contaminants are extremely potent effectors of various defence systems of higher eukaryotes, possibly because of their intrinsic function as a signal of bacterial infection. The elimination of these contaminants is a major problem in the manufacture and purification of plasmid DNA."

Further, one of ordinary skill in the art would realize that introduction of bacterial RNA, even in small amounts, might result in some level of expression of bacterial proteins within transfected cells, causing unforeseen and potentially lethal complications. As stated by Cooke et al. (page 298, second paragraph):

"The introduction to patients of plasmid or host nucleic acid sequences that are potentially oncogenic, immunogenic, or that encode antibiotic resistance genes, is of particular concern (Williams et al., 1998). As such, host RNA contamination of a recombinant therapeutic product must be minimised, particularly for therapies that require multiple patient dosing (DiPaolo et al., 1999)."

16. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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January 16, 2009